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# Melatonin for sedative withdrawal in older patients with primary insomnia: a randomized double-blind placebo-controlled trial

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## WHAT IS ALREADY KNOWN ON THIS TOPIC

- Chronic benzodiazepine-like hypnotic use is common in older adults but exposes them to risks of adverse outcomes.
- Gradual dose reduction combined with cognitive behavioural psychotherapy has been effective for benzodiazepine withdrawal, when extended over several months. However, these resource intensive interventions have limited use in clinical practice.
- There is insufficient evidence on the effects, if any, of melatonin augmentation during benzodiazepine withdrawal when combined with psychosocial support in a primary care setting.

## WHAT THIS STUDY ADDS

- Patients aged 55 years and older with primary insomnia and long term temazepam, zopiclone or zolpidem use may be tapered to discontinuation over 1 month.
- This trial compares the efficacy of controlled release melatonin and placebo, combined with psychosocial support, in withdrawal from temazepam, zopiclone and zolpidem.
- While withdrawal and sustained abstinence are feasible in a primary care setting, controlled release melatonin does not improve outcomes over placebo.

## AIM

We compared the efficacy of melatonin and placebo as adjuvants in the withdrawal of patients from long term temazepam, zopiclone or zolpidem (here 'BZD') use.

## METHODS

A double-blind, placebo-controlled, randomized trial was conducted in a primary health care outpatient clinic. Ninety-two men or women (≥55 years) with primary insomnia and chronic BZD use received controlled release melatonin 2 mg (CRM) ($n = 46$) or placebo ($n = 46$) during the 1 month withdrawal from BZDs. Psychosocial support was provided. Follow-up continued for up to 6 months. Successful BZD withdrawal by the end of 1 month was confirmed by BZD plasma determinations, while reduction in BZD use and abstinence continuing for 6 months were noted.

## RESULTS

There were two drop-outs on CRM and one on placebo. After a 1 month withdrawal, 31 participants (67%; 95% CI 54, 81) on CRM and 39 (85%; 74, 95) on placebo had withdrawn completely (intention-to-treat analysis between groups, $P = 0.051$; per protocol $P = 0.043$). Reduction in BZD use was similar or even more rare in the CRM than in the placebo group ($P = 0.052$ per protocol). After 6 months, 14 participants in the CRM group and 20 in the placebo group remained non-users of BZD (NS between groups). BZD doses were higher in the CRM than in the placebo group at the end of the 6 month follow-up ($P = 0.025$). Withdrawal symptoms did not differ between the groups.

## CONCLUSIONS

Gradual dose reduction of BZDs combined with CRM or placebo, and psychosocial support produced high short term and moderate long term BZD abstinence. CRM showed no withdrawal benefit compared with placebo.

## Introduction

Insomnia is often associated with long term benzodiazepine (BZD) use. BZD use may result in additional adverse outcomes, such as cognitive impairment, dementia, confusion and balance difficulties that may lead to falls, accidents and increased mortality [1–5]. The risks of tolerance, dependence and abuse, and the efficacy and side effects are quite similar for the three most common benzodiazepines and benzodiazepine related drugs used as hypnotics in Finland (temazepam, zopiclone and zolpidem; here in short 'BZD') [1, 6–8]. A meta-analysis of short term BDZ use in the aged (≥60 years) concluded that the risks of cognitive and psychomotor adverse outcomes are greater than the benefits [1]. Nonetheless, there is widespread BZD use in aged patients [9, 10]. The BZD related harms and strategies for their reduction have been reviewed creditably in a recent issue of this journal [11]. Pharmacological [12], non-pharmacological and combined interventions [13, 14] have been used to support withdrawal from long term BZD use. From experience with these, there is strong agreement that gradual reduction of the benzodiazepine dose (GDR) is more effective in withdrawal than is abrupt discontinuation [12–14].

The meta-analysis on BZD withdrawal interventions by Parr and co-workers dichotomized randomized trials (RCTs) as brief, GDR or psychological interventions. This meta-analysis [13] identified 32 RCTs, of which five compared brief interventions, one GDR, three psychological treatments with GDR compared with GDR only or to routine care, and others compared GDR with replacement pharmacotherapy in out-patient settings. Psychotherapeutic interventions, for example, relaxation training, psychoeducation for benzodiazepine withdrawal, instruction in self-management strategies to address insomnia and cognitive behavioural treatment of insomnia, and brief interventions with GDR resulted in follow-up withdrawal rates superior to routine care [13]. Replacement pharmacotherapies did not improve GDR outcomes, and abrupt substitution of BZD by pharmacotherapy from a different drug class was less effective than GDR alone [13]. Older patients, i.e. 60 years of age or older, were separately identified in only 10 of the 32 RCTs [13]. Despite wide age variations within and between the RCTs, no different age groups were used in the meta-analysis, reducing its external validity for older adults.

While melatonin appears relatively safe, it is controversial whether it has clinically important benefits for sleep disorders [15–18]. Melatonin, especially in a controlled release formulation (CRM) [19, 20], might be expected to safely help older long term benzodiazepine users to withdraw because of its effects on sleep as measured by wrist actinography [21], electroencephalography (EEG) and polysomnography [22].

In primary insomniacs already using benzodiazepines, CRM increased sleep quality over that with placebo [21, 23]. However, previous RCTs [24, 25] on the effect of melatonin in withdrawal from benzodiazepines have shown conflicting results. In the RCT by Garfinkel *et al*. [24], melatonin (CRM 2 mg daily) was beneficial for BZD withdrawal in a 6 week withdrawal of benzodiazepines and also when the participants openly continued melatonin use after the withdrawal period. In the RCT by Vissers *et al*. [25], there was no significant difference between melatonin 5 mg and placebo groups after a 10 week BZD withdrawal or at the 1 year follow-up.

Our hypothesis was that CRM might be beneficial in treating both withdrawal symptoms and the underlying primary insomnia that led to long term BZD use. The aim of this 1 month withdrawal trial in older adults with primary insomnia was to compare the efficacy of CRM with placebo in gradual withdrawal from chronic hypnotic use of temazepam, zopiclone or zolpidem. All participants received additional individualized sleep hygiene counselling and psychosocial support during the 1 month withdrawal period. To evaluate the persistence of withdrawal results, a 5 month follow-up was performed. Short term withdrawal symptoms during the first month's withdrawal period, long term withdrawal symptoms during the follow-up period and adverse events were assessed blindly in both groups.

## Methods

### *Study design*

We performed a randomized, double-blind, placebo-controlled, parallel group trial of CRM (Circadin® 2 mg depot tablet, RAD Neurim Pharmaceuticals EEC Limited, UK) in BZD withdrawal during a 1 month period and a double-blind 5 months' follow-up. Thus, the total duration of the study was 6 months. One tablet of Circadin® 2 mg depot is the daily melatonin dose recommended by the manufacturer for short term treatment of primary insomnia in patients aged 55 years or over. In addition, all participants received individual sleep hygiene counselling and psychosocial support during the withdrawal period. Psychosocial support and counselling were provided by a primary care physician (RL). These services included information on the causes of and the factors contributing to insomnia, possible adverse effects of long term BZD use, possible withdrawal symptoms, including rebound insomnia, basic relaxation techniques and advice on how to facilitate normal sleep. This psychosocial support was continued by a nurse (JS or MS) who provided supportive visits once a week during the withdrawal period and remained available by phone for continued advice. The study protocol was approved by the Ethics Committee of Satakunta Hospital District (2§/7/2008) and by the National Agency for Medicines of Finland (218/2008; EudraCT 2008–0006795-30). Written informed consent was received from each participant before the study began.

## Participants

Participants were primary health care outpatients living in the Province of Satakunta, in western Finland. The trial was performed in the City of Pori, at the Medical Teaching and Research Health Centre of the Department of Family Medicine, University of Turku.

Personnel working in local health centres informed patients about the study and recruited volunteers. In addition, two advertisements were placed in local newspapers. Recruiting occurred between 16 February 2009 and 14 January 2010. A nurse performed the preliminary telephone or e-mail screenings, a physician met the potential participants for screening, recruitment and obtaining written informed consent and a pharmacist (EC) randomized participants to blocks of eight to the CRM group or to the placebo group according to a predetermined ratio of 1 : 1. Randomization codes were not decoded until the end of follow-up, 23 June 2010, to ensure double-blinding during all parts of the trial, including the follow-up. Participants were compensated for their travelling expenses.

To be included, men and women aged 55 years or older had to be long term users of BZDs as hypnotics, defined as 1 month or longer regular night-time use. The three most common BZDs used as hypnotics in Finland, temazepam, zopiclone or zolpidem [26], were the focus, but they must have been prescribed according to DSM-IV criteria for primary insomnia [27].

The key exclusion criteria consisted of concurrent use of antipsychotic or anti-epileptic medications, use of a BZD other than temazepam, zopiclone or zolpidem; a history of, or active alcohol or drug abuse, severe anxiety disorder or other severe psychiatric disorder, severe neurological disease, smoking more than 10 cigarettes a day, autoimmune disease or galactosaemia or use of medication that potentially interacts with melatonin [28].

## Interventions

At baseline, a physician provided psychosocial support and individual sleep hygiene counselling, including discussions with participants about regular sleep rhythm and the influence of the following on sleep: normal changes in sleep patterns related to ageing, conditions of the bedroom and bed, exercise, eating and alcohol use, coffee and stimulants prior to sleeping, deep and calm breathing, and psychic and physical relaxation in bed and, if anxieties arise, to write them on paper. The physician performed a clinical examination of each participant and, in agreement with the participant, determined an individual withdrawal schedule. Most often the recommended reduction from the initial BZD daily dose was 50% per week. Among those participants with the highest initial BZD dose, e.g. more than twice the age-related defined daily dose (DDD) [29], the initial dose was reduced by 25% per week from the initial daily dose. Furthermore, the physician informed participants about possible withdrawal symptoms. The psychosocial support was further continued by a nurse who provided supportive visits once a week during the withdrawal period and was available for advice by phone.

## Measurements

Interviews and measurements were performed at baseline, during the 1 month withdrawal period (at weeks 1, 2, 3 and 4 from the baseline), and at month 6 after withdrawal initiation in order to assess the intervention's effects on BZD withdrawal, withdrawal symptoms and adverse events (Figure 1).

At baseline, socio-demographic data (age, gender, marital status, education, occupation) and data on health and disease were collected using questionnaires which were completed by the patient and verified by the interviewer. At baseline, mood was measured by the Geriatric Depression Scale 15 (GDS-15) [30], the scale of which was extended to cover five possibilities per question. BZD use was determined at baseline and at months 1 and 6. The Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) [31] was completed at week 1, and at months 1, 2 and 6. The nurse performed baseline measurements. Subsequent participant contacts with the nurse consisted of interviews, measurements and psychosocial support (at weeks 1, 2, 3 and 4 from the baseline). Participants also had the option during the withdrawal period (from baseline to month 1) for weekly psychosocial support sessions with the physician. The nurse's follow-up re-assessments were at months 2 and 6 after withdrawal initiation, and the physician's follow-up examination occurred at month 6 after withdrawal initiation (Figure 1).

Blood samples were drawn at baseline and at month 1 to determine plasma concentrations of temazepam, zopiclone, zolpidem, and of diazepam, desmetyldiazepam and oxazepam. Samples were taken between 10.00 h and 15.00 h. Plasma samples were kept deep-frozen until analyzed by a specific and sensitive liquid chromatographic-tandem mass spectrometric method [32]. The lower limit of quantification (LLQ) was 1.0 ng $ml^{-1}$ for temazepam and zolpidem, and 5.0 ng $ml^{-1}$ for zopiclone. The detection limits were about five times lower than the LLQ. The between-day coefficient of variation was 5–13% at relevant concentrations.

## Sample size determination

During the planning of this study, we estimated that the mean BZD dose, as diazepam equivalents $day^{-1}$, would be 6 mg at 4 weeks for the CRM group and the mean for those in the placebo group would be 15 mg, and that both groups' standard deviation (SD) would be 14 mg. Using a two-sample *t*-test with power of 80% and alpha of 0.05 (two-sided test), 39 participants were needed in each group. Using a power of 90% increased the required number of participants to 52 in each group.

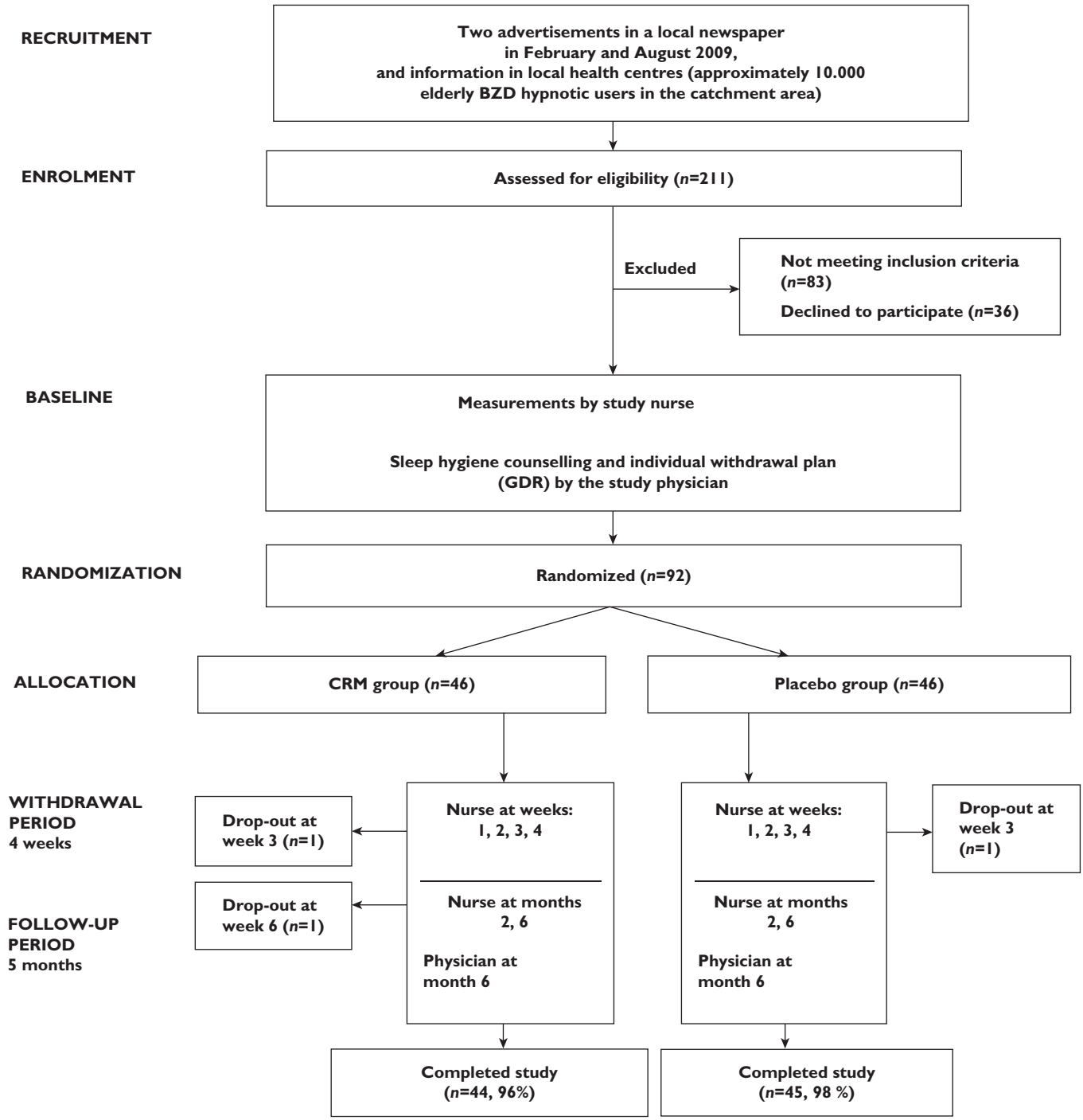


**Figure 1**

Flow of participants. GDR gradual dose reduction. CRM controlled release melatonin

For practical reasons, a total of 92 eligible participants were recruited. Power calculations were performed using nQuery Advisor 4.0.

## *Outcome measures*

The primary end point was total BZD withdrawal at the end of a 1 month withdrawal period (complete short term withdrawal). The secondary end point was the reduction of BZD use by the end of the 1 month withdrawal period in those participants who could not totally withdraw from BZDs (partial short term withdrawal). Other secondary end points were the persistence of long term withdrawal and long term reduction of BZD use at 6 months (long term withdrawal). The short term primary outcomes were

determined by interview and verified by BZD plasma concentrations at baseline and at the end of the 1 month withdrawal period. The physician determined the participant's long term withdrawal results by interview using a structured questionnaire [31] and by checking the participants' medical and prescription records for potential refills.

### Statistical analyses

Categorical variables are described as counts and frequencies and continuous variables by means and SDs or medians and ranges. Differences in continuous variables between the melatonin and the placebo groups were tested by Student's two-sample *t*-test or by the Mann–Whitney U-test, when appropriate. Variables measured with ordinal or nominal scales between the CRM group and the placebo group were tested using a Chi-square or Fisher's exact test. For selected variables 95% confidence intervals (CI) were calculated, and intention-to-treat and per protocol analyses were included. The following defined daily doses (DDD)s [29] were used to compare BZD use: (i) for participants <70 years of age, zolpidem 10 mg, zopiclone 7.5 mg, and temazepam 20 mg and (ii) for those ≥70 years, temazepam 10 mg. DDDs were categorized into five groups (0, 0.01–0.20, 0.21–0.99, 1 and >1) for statistical analyses. The differences in changes between and within the DDD groups and the frequency of patients' taking additional BZD were analyzed by cumulative logistic regression using Generalized Estimating Equations (GEE) with an independent correlation structure. The results are described as Cumulative Odds Ratios (COR) with 95% CI. The sum of withdrawal symptoms was determined according to the BWSQ [31] and then analyzed using repeated measures analysis of variance using a compound symmetry covariance structure. The group was used as a fixed effect and time as a repeated effect. The symptom sums were log-transformed for statistical analysis due to their being positively skewed. *P* values less than 0.05 were considered statistically significant.

The statistical analyses were performed using SAS version 9.2 and Enterprise Guide version 4.1 (SAS Institute Inc., Cary, NC, USA).

## Results

### Recruitment, enrolment and randomization

Altogether, 211 individuals were assessed for eligibility. Eighty-three of them (39%) did not meet the inclusion criteria and 36 (17%) declined to participate, leaving 92 eligible participants to be randomized to the CRM ($n = 46$) and placebo groups ($n = 46$) (Figure 1).

### Discontinuations during withdrawal period and follow-up

Of the 92 participants, 89 completed the 1 month withdrawal and were followed up to 6 months after initiation of the withdrawal. There were two drop-outs in the CRM group and one in the placebo group. The reasons for these discontinuations included difficulties in achieving and maintaining night-time sleep and daytime tiredness (a female in the placebo group), inability to lower the BZD dose and difficulties with sleeping (a male, high dose zopiclone user in the CRM group) and transportation impediments (a female in CRM group). The first two participants dropped out at week 3, and the last one at week 6, after completion of the withdrawal period (Figure 1). In addition, some questionnaires were incomplete, which explains that at some time points data are from 42–46 participants per group as indicated in the tables.

### Comparability of CRM and placebo groups at baseline

The CRM and the placebo groups did not differ from each other in socio-demographic data or health habits at baseline (Table 1). At baseline, 49 participants (54%) used zopiclone in daily doses ranging from 3.75 to 30 mg, 26 (28%) used zolpidem 5–20 mg and 14 (15%) used temazepam 10–30 mg, respectively. Two male participants used both zopiclone and temazepam, and one male used all these three hypnotics. Participants in the CRM and placebo groups did not differ in the duration of BZD use ($P = 0.107$), their doses in DDD (COR = 0.8, 95% CI 0.4, 1.7, $P = 0.526$) or in their residual plasma concentrations at baseline: temazepam ($P = 0.053$), zopiclone ($P = 0.402$) or zolpidem ($P = 0.237$) (Tables 1, 2 and 3).

### Efficacy of CRM compared with placebo for BZD withdrawal

*Efficacy end points at the end of a 1 month withdrawal period by plasma concentrations* After a 1 month withdrawal period, there were 31 [ITT 67% (95% CI 54, 81), per protocol 69% (95% CI 55, 82)] complete short term withdrawers in the CRM group and 39 [85% (95% CI 74, 95), per protocol 87% (95% CI 77, 97)] complete short term withdrawers in the placebo group according to plasma concentrations (between the groups: ITT analysis $P = 0.051$; per protocol analysis $P = 0.043$) (Table 3). Plasma BZD concentrations decreased to at least half of the baseline level among most non-withdrawers after the 1 month withdrawal period (Table 3).

*Efficacy end points at the end of a 1 month withdrawal period by DDD*. The change in DDD between CRM and placebo groups approached borderline significance ($P = 0.052$, Table 2). After a 1 month withdrawal period, there were 36 complete withdrawers in the CRM group and 41 in the placebo group ($P = 0.134$, per protocol analysis) (Table 2). There were no differences between the CRM and placebo groups in the number of complete withdrawers (primary end point) or dose-reducers (secondary end point) by DDD category (COR = 2.6, 95% CI 0.7, 9.2, $P = 0.136$).

## Table 1

Socio-demographic characteristics and health habits of the participants at baseline according to randomization to the melatonin (CRM) or the placebo group, and statistical comparisons between the groups

| | CRM group ($n = 46$) | | Placebo group ($n = 46$) | | |
|---|---|---|---|---|---|
| | Median | (IQR) [Range] | Median | (IQR) [Range] | *P* |
| **Age (years)** | 66.5 | (11) [55–89] | 65.0 | (10) [56–91] | 0.959 |
| **Body mass index (kg m$^{-2}$)** | 27.3 | (3.8) [21.3–41.6] | 26.4 | (6.4) [18.8–37.1] | 0.312 |
| **Doses of alcohol per week (1 dose = 12 g)** | 1.3 | (5.5) [0–39.5] | 1.1 | (4) [0–13.3] | 0.602 |
| | ***n*** | **(%)** | ***n*** | **(%)** | |
| **Women** | 27 | (59) | 34 | (74) | 0.123 |
| **Exercise (h) in a week** | | | | | |
| **<0.5 h** | 5 | (11) | 2 | (4) | 0.106 |
| **0.5–3 h** | 38 | (83) | 44 | (96) | |
| **≥3 h** | 3 | (6) | 0 | (0) | |
| **Smokers** | 6 | (13) | 1 | (2) | 0.111 |
| **Persons living alone** | 13 | (28) | 14 | (30) | 0.819 |
| **Education** | | | | | |
| **Basic** | 22 | (49) | 18 | (39) | 0.607 |
| **Professional training** | 18 | (40) | 23 | (50) | |
| **University or college** | 5 | (11) | 5 | (11) | |
| **Occupation** | | | | | |
| **Retired** | 37 | (80) | 36 | (78) | 0.854 |
| **Daytime work** | 6 | (13) | 8 | (18) | |
| **Shift work** | 3 | (7) | 2 | (4) | |
| **Persons having a driving licence** | 39 | (85) | 41 | (89) | 0.536 |
| **Duration of regular benzodiazepine use** | | | | | |
| **<5 years** | 9 | (20) | 5 | (11) | 0.107 |
| **5–10 years** | 17 | (37) | 27 | (59) | |
| **≥10 years** | 20 | (43) | 14 | (30) | |
| **Range of use** | 2–26 years | | 1.5 months–35 years | | |

IQR, interquartile range; *P*, Statistical significance of difference between CRM and placebo groups.

## Table 2

BZD use categorized as levels of defined daily dose (DDD) in the CRM and in the placebo groups at baseline, and at months 1 and 6

| DDD | Baseline *n* (%) | Month 1 *n* (%) | Month 6 *n* (%) | *P* Month 1 *vs.* baseline | P Month 6 *vs.* baseline | *P* Month 6 *vs.* month 1 |
|---|---|---|---|---|---|---|
| **CRM group** | | | | | | |
| **0** | 0 (0) | 36 (80) | 14 (32) | <0.001 | <0.001 | <0.001 |
| **0.01–0.20** | 0 (0) | 6 (13) | 16 (36) | | | |
| **0.21–0.99** | 24 (52) | 1 (2) | 12 (27) | | | |
| **1** | 15 (33) | 2 (4) | 1 (2) | | | |
| **>1** | 7 (15) | 0 (0) | 1 (2) | | | |
| **Placebo group** | | | | | | |
| **0** | 0 (0) | 41 (91) | 20 (44) | <0.001 | <0.001 | <0.001 |
| **0.01–0.20** | 0 (0) | 3 (7) | 22 (49) | | | |
| **0.21–0.99** | 18 (39) | 1 (2) | 2 (4) | | | |
| **1** | 25 (54) | 0 (0) | 1 (2) | | | |
| **>1** | 3 (7) | 0 (0) | 0 (0) | | | |

Interaction between time and groups: $P = 0.052$, cumulative logistic regression using GEE estimation. DDD values used: for zopiclone 7.5 mg night$^{-1}$, for zolpidem 10 mg night$^{-1}$ and for temazepam 20 mg night$^{-1}$ in participants aged under 70 years and temazepam 10 mg night$^{-1}$ in subjects aged ≥70 years.

## Table 3

Residual BZD agonist plasma concentrations in the melatonin (CRM) and placebo groups, at baseline and at month 1

| Study group | Residual concentrations (ng ml$^{-1}$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | | | | Month 1 | | | |
| BZD use | *n* | (%) | Median | [Range] | *n* | (%) | Median | [Range] |
| **CRM group** | 46 | | | | 45 | | | |
| **Non-users** | 0 | (0) | 0.0 | | 31 | (69) | 0.0 | |
| **Temazepam** | 9 | (20) | 1070 | [438–2160] | 5 | (11) | 517 | [24.0–1210] |
| **Zopiclone** | 23 | (50) | 97.8 | [5.2–1030] | 6 | (13) | 32.4 | [1.5–169] |
| **Zolpidem** | 14 | (30) | 13.6 | [1.1–40.0] | 3 | (7) | 3.2 | [1.0–56.1] |
| **Placebo group** | 46 | | | | 45 | | | |
| **Non-users** | 0 | (0) | 0.0 | | 39 | (87) | 0.0 | |
| **Temazepam** | 5 | (11) | 704 | [0–968] | 1 | (2) | 15.1 | [15.1–15.1] |
| **Zopiclone** | 29 | (63) | 138 | [0–518] | 4 | (9) | 19.5 | [6.0–296] |
| **Zolpidem** | 12 | (26) | 17.3 | [5.2–46.1] | 1 | (2) | 12.3 | [12.3–12.3] |

## Table 4

Frequency of taking an additional BZD during night-time awakenings in the melatonin (CRM) and the placebo groups at baseline, at month 1 (= the end of withdrawal period) and at month 6 (= the end of 5 month follow-up period). COR<1 indicates a decrease in the frequency of taking an additional BZD

| Frequency of taking additional BZD after awakenings* | Baseline | | Month 1 | | Month 6 | | Month 1 *vs.* baseline | | Month 6 *vs.* baseline | | Month 6 *vs.* month 1 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | (%) | *n* | (%) | *n* | (%) | COR (95% CI) | *P* | COR (95% CI) | *P* | COR (95% CI) | *P* |
| **CRM group** | 46 | (100) | 45 | (98) | 44 | (96) | | | | | | |
| Every night | 12 | (26) | 0 | (0) | 2 | (5) | 0.2 (0.1, 0.4) | <0.001 | 0.4 (0.2, 0.6) | <0.001 | 1.9 (1.0, 3.5) | 0.059 |
| 1–5 nights week$^{-1}$ | 4 | (9) | 5 | (11) | 6 | (14) | | | | | | |
| Less than once a week | 9 | (20) | 4 | (9) | 6 | (14) | | | | | | |
| Never or less than once a month | 21 | (46) | 36 | (80) | 30 | (68) | | | | | | |
| **Placebo group** | 46 | (100) | 45 | (98) | 44 | (96) | | | | | | |
| Every night | 8 | (17) | 0 | (0) | 0 | (0) | 0.1 (0.0, 0.4) | <0.001 | 0.1 (0.0, 0.2) | <0.001 | 0.6 (0.1, 2.8) | 0.502 |
| 1–5 nights week$^{-1}$ | 6 | (13) | 2 | (4) | 1 | (2) | | | | | | |
| Less than once a week | 10 | (22) | 3 | (7) | 2 | (5) | | | | | | |
| Never or less than once a month | 22 | (48) | 40 | (89) | 41 | (93) | | | | | | |

*Interaction between time and groups; $P = 0.031$; cumulative logistic regression using GEE estimation. CI, confidence interval; COR, cumulative odds ratio.

*Efficacy end points at month 6.* At month 6 after withdrawal initiation, there were 14 (32%) complete withdrawers in the CRM and 20 (44%) in the placebo group ($P = 0.220$, per protocol analysis). There was more BZD usage by DDD in the CRM group compared with the placebo group (COR = 2.5, 95%, CI 1.1, 5.5, $P = 0.025$) (Table 2).

### *Use of an additional BZD after night-time awakenings*

At baseline, 12 participants in the CRM group and eight in the placebo group reported taking an additional BZD after awakening each night ($P = 0.593$). During the withdrawal period, the frequency of taking an additional BZD during the night decreased in both groups but there was no significant difference between the groups (Table 4). At the end of the follow-up periods, the reduction in additional BZD use for night-time awakenings, compared with the baseline, was still significant in both groups. However, the participants in the CRM group more frequently took an additional BZD than did those in the placebo group (COR = 6.6, 95% CI 1.7, 24.9, $P = 0.006$) (Table 4).

### *Withdrawal symptoms and safety during withdrawal and follow-up*

The occurrence of withdrawal symptoms assessed with the BWSQ [31] did not differ between the CRM and placebo groups at week 1 or at months 1 and 6 (Table 5). There was no serious adverse outcome in either group during the withdrawal period or at follow-up.

## Discussion

CRM given during the 1 month BZD withdrawal period for participants with primary insomnia and long term BZD use

## Table 5

Comparison of the sums of withdrawal symptoms according to BWSQ between the melatonin (CRM) and the placebo groups at week 1, month 1 and month 6

| Sum of withdrawal symptoms | Week 1 *n* | Week 1 Median (IQR) [Range] | Month 1 *n* | Month 1 Median (IQR) [Range] | Month 6 *n* | Month 6 Median (IQR) [Range] | $P^1$ | $P^2$ | $P^3$ |
|---|---|---|---|---|---|---|---|---|---|
| **CRM group** | 46 | 4.1 (3.6) [0–14] | 43 | 3.2 (2.9) [0–13] | 44 | 3.6 (3.0) [0–14] | 0.886 | 0.323 | 0.198 |
| **Placebo group** | 46 | 4.0 (4.9) [0–22] | 42 | 3.2 (3.8) [0–13] | 43 | 3.1 (2.8) [0–10] | | | |

IQR, interquartile range; $P^1$, statistical significance for group × time interaction effect, repeated measures analysis of variance; $P^2$, statistical significance for group effect; adjusted for group, repeated measures analysis of variance; $P^3$, statistical significance for time effect, adjusted for time, repeated measures analysis of variance.

showed no superiority over placebo. Neither complete short term BZD withdrawal nor BZD reduction rates favoured the CRM group over the placebo group. By month 6 after withdrawal initiation, BZD use increased in both groups but, unexpectedly, there were even more withdrawers and greater BZD reduction rates in the placebo group participants than in the CRM group. BZD withdrawal symptoms in CRM users were similar to those in the placebo group and CRM did not reduce the use of an additional BZD after night-time awakenings any more than did placebo. BZD withdrawal results were good (67–85%) in both groups in the short term, though only moderate (30–43%) in the long term, suggesting that success in BZD withdrawal or dose reduction can be achieved in primary care when sufficient psychosocial support and counselling are provided.

Our results agree with two previous RCTs [25, 33] which showed no significant difference between melatonin and placebo in short term BZD withdrawal outcomes. In contrast to our results, a previous RCT [24] using CRM 2 mg nightly for 6 weeks reported significantly better BZD discontinuation than did placebo. Our intervention showed only moderate, long term BZD withdrawal rates. Garfinkel *et al*. [24] reported a very high (78%) persistence of BZD withdrawal in the CRM group. In that study, however, study participants received open label CRM for up to 6 months, while our participants received CRM only during the 1 month withdrawal period. This longer CRM use may partly explain the difference in outcomes. Comparisons with previously published RCTs [24, 25, 33] must be made with caution due to subtle but meaningful methodological differences in design, length of melatonin treatment, use of melatonin during follow-up and measures reported. Previous RCTs have been performed with small samples, ranging from 34 to 45 participants, without reporting power calculations for those sample sizes and the difference [25] in preparations (controlled release [24], fast release [25, 33]) and doses of melatonin (2 mg [24], 3 [33], 5 [25]) studied. Furthermore, those samples have included participants younger than 55 years [24, 25, 33] and/or they have not reported the age range or inclusion criteria concerning the younger age group [33]. GDR has been shown to be useful in BZD withdrawal [12–14]. Some of the previous melatonin RCTs and our study combined GDR with melatonin treatment during the withdrawal phase. Our short term withdrawal results were good in both the CRM and placebo groups. We suggest that these results are explained by including intensive psychosocial support during the withdrawal period in participants sufficiently motivated to withdraw to participate voluntarily in the study. Furthermore, in primary care settings like this trial, patients may be less likely to try to evade an intervention provided by the team that is coordinating their care and whom they regularly see the most.

In previous BZD withdrawal trials [12] the drop-out rate varied between 18 and 73%. In an open trial [34] assessing the efficacy of CRM, only 96 of the 244 (43%) participants completed the 12 month follow-up. Previous studies that combined GDR and cognitive behavioural therapy (CBT) reported drop-out rates from 3 to 28%, while withdrawal studies with GDR alone had drop-out rates between 12 to 22% [13, 14]. Our trial had a minimal number of drop-outs compared with the combination CDR and CBT studies. We suggest that this is due to providing psychosocial support during the withdrawal period and that most participants were highly motivated to withdraw from BZD use. When they were told that BZD withdrawal symptoms are temporary and would pass, many participants even accepted being awake for 2 or 3 nights during the withdrawal period. We think that an additional key factor for the low drop-out rate was the possibility for counselling and support by phoning the nurse or making extra visits to the nurse. Once a week appointments with the nurse appeared to be sufficiently supportive during the withdrawal period, but it is possible that most participants may have required even more support after the withdrawal period to accomplish healthier sleep patterns without BZDs. It is speculative but reasonable to infer that if psychosocial support had been provided during the follow-up period, long term persistence and withdrawal rates may have been higher.

Why was CRM not superior to placebo? Long term BZD dependence may be more adverse for sleep quality than the compensatory effects of a 2 mg dose of CRM are for sleep improvement. Paradoxically, a previous RCT [33] found sleep quality to be worse in the CRM group compared with the placebo group during the first weeks of BZD withdrawal, while in other studies sleep quality was improved by using CRM in BZD users [21, 23]. A placebo effect may be operating both in the use of BZDs for insomnia and in BZD withdrawal [8]. However, our present RCT design did not allow us to study the possible significance of a placebo effect in BZD withdrawal as there was no internal control group with only a pharmacological or a psychosocial intervention. Therefore we cannot distinguish medication effects from those due to psychosocial support [35, 36]. However, we suggest that, for patients, a tablet provides psychological benefit when withdrawing from long term BZD use.

### *Strengths and weaknesses of the study*

Randomization and double-blinding were successful, so our CRM and placebo groups were comparable from the baseline until the end of follow-up. The preparations given to participants had an identical appearance, ensuring the double-blinding. Not all participants could remember when they had started to use BZD as a hypnotic. By checking prescriptions from each participant's health centre and hospital documents and by consulting with the participant's physician, we could estimate the duration by classifying use as less than 5 years of BZD use, from 5 to 10 years and 10 or more years of BZD use. There were only two participants who had used BZD for less than 1 year. We used two methods to determine the change in BZD use. BZD concentrations were drawn at baseline and at the end of withdrawal period. Additionally, BZD use was assessed via interview and converted to DDD at baseline, 1 and 6 months. According to the BZD plasma concentrations, five participants in the CRM group and two in the placebo group have misrepresented their discontinuation of BZDs. This phenomenon has been reported previously [25]. Additionally, it is possible that very small residual concentrations may not have been detected or that plasma concentrations have varied due to different sampling times. These can explain the minor differences in results between the two methods for determining BZD use at baseline and after completion of the withdrawal period. The reliability of persistence of long term BZD withdrawal results would have been improved if the concentrations had been drawn at follow-up months 2 and 6 also.

In conclusion, CRM or placebo combined with a gradual BZD withdrawal programme, sleep hygiene counselling and psychosocial support can produce high short term BZD withdrawal and reduction rates and moderate long term abstinence rates in older patients. CRM 2 mg does not offer an advantage over placebo for patient withdrawal from long term BZD use for treatment of primary insomnia.

## Competing Interests

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All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare RL is a shareholder of Orion. JP has lectured in continuing education courses sponsored by Boehringer-Ingelheim, Lundbeck, Novartis and Orion. TV has no competing interests. AL has served on Advisory Boards for or consulted with Novo Nordisk, Pfizer and Sanofi-Aventis Groupe. PP-K has lectured in continuing education courses sponsored by Vichy. PJN is a shareholder of Orion. MP has received honorariums for lecturing from Cephalon, Glaxo Smith Kline, Leiras-Nycomed, Servier and UCB and has been a member of the Medical Advisory Board of UCB. IR has given lectures in continuing education courses sponsored by Novartis and Janssen-Cilag. SLK has given lectures in continuing education courses sponsored by Lundbeck, Ratiopharm and Leiras. There are no other relationships or activities that could appear to have influenced the submitted work.

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## REFERENCES

**1** Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ 2005. doi:10.1136/bmj.38623.768588.47

**2** Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 2004; 18: 37–48.

**3** Barker MJ, Greenwood KM, Jackson M, Crowe SF. An evaluation of persisting cognitive effects after withdrawal from long-term benzodiazepine use. J Int Neuropsychol Soc 2005; 11: 281–9.

**4** Gallacher J, Elwood P, Pickering J, Bayer A, Fish M, Ben-Shlomo Y. Benzodiazepine use and risk of dementia: evidence from the Caerphilly Prospective Study (CaPS). J Epidemiol Community Health 2012; 66: 869–73.

**5** Billioti de Gage S, Begaud B, Bazin F, Verdoux H, Dartigues JF, Peres K, Kurth T, Pariente A. Benzodiazepine use and risk of dementia: prospective population based study. BMJ 2012; 345: e6231.

**6** Siriwardena AN, Qureshi MZ, Dyas JV, Middleton H, Orner R. Magic bullets for insomnia? Patients' use and experiences of newer (Z drugs) versus older (benzodiazepine) hypnotics for sleep problems in primary care. Br J Gen Pract 2008; 58: 417–22.

**7** NICE. Guidance on the Use of Zaleplon, Zolpidem and Zopiclone for the Short-Term Management of Insomnia. London: National Institute for Clinical Excellence, 2004.

**8** Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. BMJ 2012; 345: e8343.

**9** Jyrkka J, Vartiainen L, Hartikainen S, Sulkava R, Enlund H. Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+Study. Eur J Clin Pharmacol 2006; 62: 151–8.

**10** Puustinen J, Nurminen J, Lopponen M, Vahlberg T, Isoaho R, Raiha I, Kivela SL. Use of CNS medications and cognitive decline in the aged: a longitudinal population-based study. BMC Geriatr 2011; 11: 70.

**11** Lader M. Benzodiazepine harm: how can it be reduced. Br J Clin Pharmacol 2014; 77: 295–301.

**12** Denis C, Fatseas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database Syst Rev 2006; (3)CD005194.

**13** Parr JM, Kavanagh DJ, Cahill L, Mitchell G, Mc DYR. Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. Addiction 2009; 104: 13–24.

**14** Voshaar RC, Couvee JE, van Balkom AJ, Mulder PG, Zitman FG. Strategies for discontinuing long-term benzodiazepine use: meta-analysis. Br J Psychiatry 2006; 189: 213–20.

**15** Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, Ford I. Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev 2005; 9: 41–50.

**16** Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Baker G, Klassen TP, Vohra S. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med 2005; 20: 1151–8.

**17** Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS ONE 2013; 8: e63773.

**18** Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, Vohra S, Klassen TP, Baker G. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ 2006; 332: 385–93.

**19** Lemoine P, Wade AG, Katz A, Nir T, Zisapel N. Efficacy and safety of prolonged-release melatonin for insomnia in middle-aged and elderly patients with hypertension: a combined analysis of controlled clinical trials. Integr Blood Press Control 2012; 5: 9–17.

**20** Lemoine P, Zisapel N. Prolonged-release formulation of melatonin (Circadin) for the treatment of insomnia. Expert Opin Pharmacother 2012; 13: 895–905.

**21** Garfinkel D, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet 1995; 346: 541–4.

**22** Luthringer R, Muzet M, Zisapel N, Staner L. The effect of prolonged-release melatonin on sleep measures and psychomotor performance in elderly patients with insomnia. Int Clin Psychopharmacol 2009; 24: 239–49.

**23** Garfinkel D, Laudon M, Zisapel N. Improvement of sleep quality by controlled-release melatonin in benzodiazepine-treated elderly insomniacs. Arch Gerontol Geriatr 1997; 24: 223–31.

**24** Garfinkel D, Zisapel N, Wainstein J, Laudon M. Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. Arch Intern Med 1999; 159: 2456–60.

**25** Vissers FH, Knipschild PG, Crebolder HF. Is melatonin helpful in stopping the long-term use of hypnotics? A discontinuation trial. Pharm World Sci 2007; 29: 641–6.

**26** FIMEA. Finnish Medicines Agency: drug consumption statistics 2007–2010 (in Finnish). Helsinki, Finland, 2011.

**27** APA. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington, DC: American Psychiatric Association, 1994.

**28** Pharmaca Fennica 2008. Pharmaceutical Information Centre (Lääketietokeskus), Helsinki, Finland, 2008.

**29** National Agency of Medicines. Classification of Medicines (ATC) and Defined Daily Doses (DDD). Helsinki, Finland: National Agency for Medicines, 1996.

**30** Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry 1999; 14: 858–65.

**31** Tyrer P, Murphy S, Riley P. The Benzodiazepine Withdrawal Symptom Questionnaire. J Affect Disord 1990; 19: 53–61.

**32** Quintela O, Sauvage FL, Charvier F, Gaulier JM, Lachatre G, Marquet P. Liquid chromatography-tandem mass spectrometry for detection of low concentrations of 21 benzodiazepines, metabolites, and analogs in urine: method with forensic applications. Clin Chem 2006; 52: 1346–55.

**33** Cardinali DP, Gvozdenovich E, Kaplan MR, Fainstein I, Shifis HA, Perez Lloret S, Albornoz L, Negri A. A double blind-placebo controlled study on melatonin efficacy to

reduce anxiolytic benzodiazepine use in the elderly. Neuro Endocrinol Lett 2002; 23: 55–60.

**34** Lemoine P, Garfinkel D, Laudon M, Nir T, Zisapel N. Prolonged-release melatonin for insomnia – an open-label long-term study of efficacy, safety, and withdrawal. Ther Clin Risk Manag 2011; 7: 301–11.

**35** Macedo A, Farre M, Banos JE. Placebo effect and placebos: what are we talking about? Some conceptual and historical considerations. Eur J Clin Pharmacol 2003; 59: 337–42.

**36** Shorter E. A brief history of placebos and clinical trials in psychiatry. Can J Psychiatry 2011; 56: 193–7.